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CRANE, EXAMINER

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ART UNIT	PAPER NUMBER
1803	5

DATE MAILED: 10/02/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 05/24/95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ------ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-70 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 1-70 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).

12. ☒ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☒ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.

13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group 1800, Art Unit 1803.

Claims **1-70** remain in the instant case.

The non-statutory double patenting rejection, whether of the obvious-type or non-obvious type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thompson,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel,* 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam,* 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi,* 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman,* 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 C.F.R. §§1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with the application. See 37 C.F.R. §1.78(d).

Effective January 1, 1994, an registered attorney or agent of record may sign a Terminal Disclaimer. A Terminal Disclaimer signed by the assignee must fully comply with 37 C.F.R. §3.73(b).

Claims **1-70** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the prior invention as set forth in claims **1-7 and 11-12** of prior U.S.

Patent No. **4,806,263**. Although the conflicting claims are not identical ('263 claims "therapeutic compositions" and "methods of treating HTLV-III" and herein are claimed "compounds", "pharmaceutical compositions" and "methods of treating HTLV-III"), they are not patentably distinct from each other because the instant claims are directed to a portion of the subject matter claimed in the noted patented claims. As to the portion of the subject matter not claimed in the prior patent, namely "compounds", applicant is referred to *Ex Parte Billman*, 71 USPQ 253 wherein it is stated that "[whether]...the effective ingredient ... is carried by a solvent or a diluent does not change the effective character of the compound." This view is further supported by the more recent decision in *In re Rosicky*, 125 USPQ 341 wherein it is stated that "A known compound in association with a carrier is not a patentable composition." Therefore, it is presumed that the inverse proposition is also valid and renders the instant "compound" claims obvious in view of the patented pharmaceutical composition claims.

Claims **1-64** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1-6** of allowed U.S. Application No. **07/882,073**. Although the conflicting claims are not identical, they are not patentably distinct from each other because allowed claims **1-6** are directed only to oligonucleotide analogues effective to inhibit replication or gene expression of HTLV-III, while claims **1-64** are drafted to include oligonucleotide analogues capable of inhibiting of replication or gene expression of an "infectious agent", specifying that agent to be HTLV-III in some claims, and pharmaceutical compositions thereof. As to the portion of the subject matter not claimed in the prior patent, namely "pharmaceutical compositions", applicant is

referred to *Ex Parte Billman*, 71 USPQ 253 wherein it is stated that "[whether]...the effective ingredient ... is carried by a solvent or a diluent does not change the effective character of the compound." This view is further supported by the more recent decision in *In re Rosicky*, 125 USPQ 341 wherein it is stated that "A known compound in association with a carrier is not a patentable composition."

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

The specification is objected to under 35 U.S.C. §112, first paragraph, as failing to teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

Appellant's specification fails to provide sufficient guidance or support to enable the worker of ordinary skill in the art to use the disclosed antisense oligonucleotide analogues as alleged, the administration of the instant antisense oligonucleotide analogue-containing pharmaceutical compositions to hosts infected with manifold different viral infections, HIV and hosts in need of treatment for a tumor. The specification describes the alleged treatments in a prophetic manner only. Such allegations are not considered to provide a basis for presuming or establishing activity *in vitro* or *in vivo*, particularly since numerous additional factors present *in vivo*

are not accounted for, including enzymes, hormones, transport proteins, messengers, etc.

Further, there is no enabling description of the administration of any instant pharmaceutical compositions. The worker of ordinary skill in the art would not be able to practice the instantly claimed methods of treatment given the limited guidance provided by the disclosure herein provided. The mere statements that the compounds of the instant invention are likely to be effective, or expected to be effective, are insufficient to enable the worker of ordinary skill in the art to practice the invention. It is well known and established that "law requires that disclosure in an application shall inform those skilled in the art how to use appellant's alleged discovery, not how to find out how to use it for themselves." *In re Gardner et al.*, 166 USPQ 138 (CCPA 1970).

Appellant has proposed a mechanism (antisense) by which the claim designated oligonucleotide analogues could possible act to interfere with the biochemical effects of RNA or DNA and thereby create a desired pharmaceutical effect. However, the disclosure fails to describe or teach how to get the claimed compounds to a locus to permit them to act as described. Further, the disclosure provides no guidance as to how to obtain a "therapeutically" effective amount at the locus of action. Moreover, there is no evidence that any "antisense" mechanism of action has ever been successfully used to treat any condition such as those enumerated in the specification or implied by the claims. Absent such guidance it would not be possible to practice the invention. Appellant is referred to the Zon reference, at p. 546, second column, "Practical Considerations", which discloses results through circa 1988 and, as noted in the rejection supra

makes prophetic speculations concerning the future of "antisense" oligonucleotides as chemotherapeutic agents *in vivo*

Absent any data, clearly correlative to the alleged uses, demonstrating the claimed method, the person having ordinary skill in the art would not be able to practice the instant invention without an undue amount of experimentation and speculation, since many agents which provide exceptional results *in vitro* are ineffective *in vivo*, due to the high degree of unpredictability in this art.

For the reasons set forth above, and in view of the contemporary knowledge in this art, it has been established herein that those persons skilled in the art at the time of the present invention i) would not accept the mere allegation of medicinal activity as set forth in the instant specification as a basis for concluding that the claimed oligonucleotide analogues would exhibit either *in vitro* or *in vivo* efficacy in the treatment of any viral, retroviral and/or neoplastic disease conditions, ii) would not equate such prophetic disclosures in the instant art with an expectation of *in vivo* activity (*Ex parte Aggarwal*, 23 USPQ 2d 1334, 1338 (BPAI 1992)), and iii) would not be able to practice the invention as described herein as required by statute.

With regard to the compound claims, it is noted that the only disclosed utility for these compounds is the *in vitro* treatment of HIV and this use is not enabled for reasons set forth above. Thus the claims to the compounds fail to comply with the use requirement of 35 U.S.C. §112, first paragraph.

Claims **59–70** are rejected under 35 U.S.C. §112, first paragraph, for the reasons set forth in the objection to the specification.

Claims **1–70** are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims **1, 9 and 17** the term "consisting essentially of" is incorrect as said term is reserved for use with compositions, but is not proper in claims directed exclusively to compounds.

In claim **25** the term "the region of the HTLV-III encoding a frameshift" is indefinite in view of the inability of applicant or of any practitioner to forecast or to otherwise specify the resultant sequences.

In claims **28–54** the term "the modified internal phosphate group is a phosphorothioate group" appear to be inconsistent with the claims from which they depend by their use of the definite article ("the"), a usage which would appear to exclude multiple phosphorothioate diester replacements of phosphodiester linkages.

As all of claims **59–64** include either a "pharmaceutically" or "therapeutically suitable carrier", applicant is requested to amend said claims to be internally consistent in style; e.g. --A pharmaceutical composition ... comprising ... and a pharmaceutically suitable carrier.--. Such an amendment should also include excision of all superfluous language directed to the intended use of the active

ingredient-containing pharmaceutical composition specified, as such language is only appropriate in method of treatment claims.

The following is a quotation of 35 U.S.C. §103 which forms the basis for all obviousness rejections set forth in this Office action:

> "A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person."

Claims **1-27 and 59-61** are rejected under 35 U.S.C. §103 as being unpatentable over Ts'o et al. '863 (PTO-892 cite "A").

The instant claims are directed to modified oligonucleotides complementary to (aka "antisense") the DNA or RNA necessary for the replication and/or gene expression of an infectious agent and incorporating one or more modified phosphate diester linkages within the modified oligonucleotide chain and pharmaceutical compositions thereof. In claims **17-27** the infectious agent is specified to be HTLV-III, a human-specific retrovirus, but none of the noted claims specify the type of "modification" which distinguishes these oligonucleotides from naturally occurring nucleic acids.

Ts'o et al. '863 in its abstract states "[o]ligonucleoside alkyl- or aryl phosphonates are non-ionic analogues of nucleic acids which possess unique physical and biological properties. These properties enable the analogues [as pharmaceutical compositions] to enter living cells intact and to bind with specifically selected nucleic acids within the cell. As a result, the analogues can specifically inhibit the function or expression of a preselected nucleic acid sequence. Thus the analogues could be used to specifically inhibit the growth of tumor cells or replication of viruses in infected cells."(emphasis added).

While Ts'o does not specifically disclose the same "antisense" oligonucleotide analogues as are herein disclosed, the instant claims are drafted with functional language which fails to specify the precise nature of the oligonucleotide analogue's "modification" and in some cases its intended target. Therefore, any modified oligonucleotide, such as those of Ts'o et al., which is disclosed to effect "replication" and "[gene] expression" in an "infectious agent" is deemed to fall within at least a portion of the instant claimed subject matter and render same lacking in patentable distinction. And since HTLV-III is nominally a "virus", the mention of "viruses" as target of antisense oligonucleotide analogues in the Ts'o et al. abstract quoted supra is deemed to have taught this alternative to any practitioner reasonably skilled in the art.

Therefore, the instant claimed oligonucleotide analogues would have been obvious to one of ordinary skill in the art having the above cited references before him at the time the invention was made.

Papers related to this application may be submitted to Group 1800 via facsimile transmission(FAX). The transmission of such papers must conform with the notice published in the Official Gazette (1096 OG 30, November 15, 1989). The telephone number for the FAX machine now on-line in Group Art Unit 1803 is (703) **308-4227** .

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E. Crane whose telephone number is 703-**308-4639** . The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Douglas W. Robinson, can be reached on (703)-308-2897.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1800 receptionist whose telephone number is 703-**308-0196** .

LECrane:lec
9/25/95

L. Eric Crane
Patent Examiner
Group 1800